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Visual scoring of non-cavitated caries lesions and clinical trial efficiency, testing xylitol in caries active adults

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Abstract

Objectives—To better understand the effectiveness of xylitol in caries prevention in adults, and to attempt improved clinical trial efficiency.

Methods—As part of the Xylitol for Adult Caries Trial (X-ACT), non-cavitated and cavitated caries lesions were assessed in subjects who were experiencing the disease. The trial was a test of the effectiveness of 5 grams/day of xylitol, consumed by dissolving in the mouth five 1 gram lozenges spaced across each day, compared with a sucralose placebo. For this analysis, seeking trial efficiency, 538 subjects aged 21–80, with complete data for four dental examinations were selected from the 691 randomized into the three year trial, conducted at three sites. Acceptable inter and intra examiner reliability before and during the trial was quantified using the kappa statistic.

Results—The mean annualized non-cavitated plus cavitated lesion transition scores in coronal and root surfaces, from sound to carious favoured xylitol over placebo, during the three cumulative periods of 12, 24, and 33 months, but these clinically and statistically non-significant differences declined in magnitude over time. Restricting the present assessment to those subjects with a higher baseline lifetime caries experience showed possible but inconsistent benefit.

Conclusions—There was no clear and clinically relevant preventive effect of xylitol on caries in adults with adequate fluoride exposure when non-cavitated plus cavitated lesions were assessed. This conformed to the X-ACT trial result assessing cavitated lesions. Including non-cavitated lesion assessment in this full scale, placebo controlled, multi site, randomized, double blinded clinical trial in adults experiencing dental caries, did not achieve added trial efficiency or demonstrate practical benefit of xylitol.

Trial Registration—ClinicalTrials.Gov NCT00393055

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Keywords

Xylitol; Dental Caries Prevention; Randomized Controlled Trial; Adults; Early Caries Lesion; Clinical Trial Efficiency; non-cavitated caries lesion

Introduction

A consensus conference (1) has called for methods for shorter and less costly clinical trials so that more caries preventive agents may be tested for efficacy and effectiveness. With a better evidence base, new preventive agents may be more confidently advocated and more widely used in public health programs and by individuals. In vitro and in vivo equivalence tests, which do not provide direct evidence of clinical efficacy, have taken precedence for established preventive agents and are not applicable for new agents. Shorter trials are likely to be more feasible when using participants with higher caries activity and incidence, but then the results will be less generalizable to the whole population. One way to make these trials more cost effective may be to employ different methods than visual cavitated caries lesion assessment (2, 3, 4). Another strategy may be to use visual assessments at earlier stages of the caries lesion's progressive but initially reversible continuum (1, 5, 6, 7).

An important aspect of efficacy in caries prevention involves not only the agent's ability to inhibit the progress to cavitation (D_2), but also in promoting the prevention, arrest or reversal of visible but non-cavitated (D_1) lesions. Such effects also occur at even earlier mineral dissolution stages that are not visible. All of these possibilities could result in fewer lesions at all stages. Traditional cavitated lesion assessment takes no specific account of such multifaceted arrest and remineralisation. Yet these are features of the disease with potential to be harnessed for prevention. Xylitol may have such preventive attributes involving remineralisation (8). There are several proposed indirect mechanisms through which xylitol could be associated with enhanced remineralisation and decreased demineralisation (9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23). Recent metabolomic analysis in vivo suggests that xylitol is not an inhibitor of plaque metabolism in acid production, but acts as a non-fermentative sugar alcohol (24). Thus some proposed mechanisms may have to be reconsidered.

The Xylitol for Adult Caries Trial (X-ACT) tested the hypothesis that daily use of xylitol lozenges (5 grams/day) will reduce dental caries incidence in caries-active adults. Evidence for xylitol efficacy from systematic reviews is controversial and unresolved (23, 25, 26, 27, 28, 29, 30, 31, 32). The effectiveness at the level of combined cavitated coronal and root lesions (D_2) and safety outcomes from this trial have been published (33). Subjects showed no consistent, significant or clinically meaningful benefit from xylitol, for coronal and root lesions combined, when this was assessed at the cavitated lesion threshold. Xylitol was however shown to prevent D_2 level root caries in this trial (48). Relatively few root lesions developed in these subjects and this effect was only apparent in this tooth surface specific analysis. The X-ACT trial also included caries assessments at the non-cavitated level for crown and root lesions (D_1) as part of an explicit aim to determine if the use of such assessments might have led to earlier results than the D_2 based analysis. Criteria were

derived from the International Caries Detection and Assessment System (34, 35). No attempt was made to distinguish between active and inactive lesions as additionally prescribed by ICDAS.

The reliability of ICDAS and related assessment methods has not been fully established for application in clinical trials, within and between multiple clinical examiners at several sites and over several years. There have been other validation and reliability tests of the ICDAS and Nyvad proposed systems of caries lesion assessment, which include early lesions (3, 36, 37, 38). A one year test of ICDAS criteria, though in differing groups of children and with very close repeat examinations, showed good to excellent inter- and intra-examiner reliability for lesion severity (39). These reliability tests do not fully exemplify and satisfy the multiexaminer, multisite and duration demands of full scale clinical trial calibrations (35). Two clinical trials have been completed using ICDAS based criteria. One unreported study assessed only two teeth per subject, not caries of each tooth surface in the whole dentition (40). Another with three clinical assessments showed no efficiency benefit over 13 months, by including non-cavitated lesions (41).

Thus the aims of this paper are:

1. To determine if a result of the trial using D_1 plus D_2 lesion data could have been obtained in the first or second year of the three year trial;
2. To contrast these results to that obtained at the more advanced and traditional caries lesion stage (D_2) after one, two, and three years; and
3. To determine if trial subjects with higher initial caries scores, and presumed to have higher caries activity, showed a greater caries preventive effect of xylitol using D_1 plus D_2 lesion level data over one, two, and three years.

Materials and Methods

The design and methods of the X-ACT trial have been published (42) including subject recruitment, caries scoring matrices, safety monitoring, power and samples size estimates and analytic methods. The caries criteria, examiner training methods and reliability assessments have also been described and assessed (35), including those involving both D_1 and D_2 level lesions, and are not repeated here.

There were three clinical study sites for X-ACT at the University of North Carolina-Chapel Hill (UNC), the University of Alabama-Birmingham (UAB), and the University of Texas Health Science Center – San Antonio (UTHSC-SA). The Kaiser Permanente Center for Health Research-Portland Oregon (KPCHR) served as the Data Coordinating Center. The study was approved by the Institutional Review Board at each of the four participating institutions and all participants provided informed consent in writing.

Inclusion criteria were age 21–80 years, the presence of at least one coronal or root surface cavitated caries lesion (present at screening, or documented in the patient record or by self-report as having been restored in the previous year), presence of at least 12 teeth, ability to read and understand English, and ability to give informed consent. Exclusion criteria were

the presence of extensive caries (more than 10 teeth with lesions), periodontal disease requiring aggressive treatment, residing in same household with another participant, or anticipated moving within three years. A total of 691 individuals met these criteria and were randomized into the study. From these we excluded 10 subjects randomized in error (part of dual households), an additional 5 subjects with missing data for other variables used in the analyses and for this report 138 subjects who failed to attend all the dental examinations. This left a total of 538 subjects with complete data (78% of the original subjects) for this analysis.

To select all subjects could have caused the result to reflect any possible systematic trends in non-participation in these timed examinations. By selecting full participants only, the results relate to time frame, not dropout effects plus time frame. This also avoided complexities in imputing missing data over three time periods, versus one period of 33 months as was done for the D_2 level outcome analysis. There was moreover, no “intent to treat” for the purpose of this particular analysis, so it seemed reasonable to select only those subjects with complete data at all four time points.

Subjects were asked to dissolve five lozenges in the mouth daily, each containing 1 gram of xylitol or a placebo of identical size, shape, color and flavor (peppermint), containing sucralose which, unlike xylitol, lacks clinically demonstrated cariostatic or cariogenic properties. These were not commercial products, but formulated for the trial. Sucralose, but not xylitol, has been shown in vitro to affect glucosyltransferases (43), but has no known effect on caries itself in animal models or in humans. Both test and placebo could equally have replaced some sugars in the diet, and caused some salivary stimulation, which might relate to caries increment.

Trained and calibrated examiners visually identified caries lesions by using a CPITN-E probe, a non-magnifying plane mirror, and standard dental operating light and chair. Loupes were used at the discretion of the examiner, but consistently within each examiner. Tooth surfaces were dried for five seconds with an air/water syringe. Examiners used a modification of the International Caries Detection and Assessment System criteria (34), with two disease levels possible for each coronal surface; sound (S), non-cavitated enamel lesion (D_1) (ICDAS codes 1 & 2): cavitated lesion penetrating the enamel (ICDAS code 3) plus cavitated lesions penetrating into dentin or “shadowing” (ICDAS codes 4, 5 and 6), combined in this report as D_2. Root surfaces were scored as sound (S), lesion with estimated depth <0.5mm (D_1), and lesion with estimated depth ≥0.5mm (D_2). Other surface conditions noted were pit and fissure sealants (P), restorations (F), crowns (C), missing teeth (M), and surfaces unable to be scored (Y). Examiners made one classification per tooth surface, and each tooth was deemed to have five coronal (including the incisal) surfaces and up to four root surfaces if exposed.

A primary examiner at each clinical center completed almost all examinations with a recorder; 100% at UAB, 98% at UNC, and 96% at UTHSC-SA, although back-up examiners were available as needed. To the extent possible, all follow-up examinations were performed by the same examiner who conducted the baseline examination. Primary and back-up examiners and recorders from all three clinical centers participated in a four-day training and

calibration session with a benchmark examiner (35), as well as refresher sessions prior to the 12-, 24-, and 33-month examinations, the study being shortened by three months in the third year. All primary examiners completed second examinations of approximately 5% of participants annually to determine intra-examiner reliability.

For this analysis the impact of the xylitol lozenges on two separate outcomes was compared; the cumulative cavitated and non-cavitated Decayed or Filled Surface ($D_{12}FS$) increment and the cumulative cavitated Decayed or Filled Surface (D_2FS) increment. The cumulation periods were 0–12 months, and 0–12+12–24 months and 0–12 +12–24 + 24–33 months, increments then being annualised for comparability. The transition weighting matrices for each score are described and justified elsewhere, (42) and both increment scores were for root and coronal surfaces combined.

Several measures were created to characterize participants at baseline and their oral health and oral healthcare practices. These included race/ethnicity, age, gender, a binary indicator of a routine dental visit (exam or cleaning) in the past year; a two-level indicator of fluoride use (in toothpaste or professional topical fluoride, or both), two indicators of oral hygiene practices (brushing and flossing) and self-reported dry mouth. All three clinical study sites are served by community water fluoridation. Forms used for all data collection are available on the study's public website, http://www.xactstudy.org

For purposes of analysis, the increment data was Winsorised constraining outlying values to be no smaller than the 1st or larger than the 99th percentiles. Because the $D_{12}FS$ lesion transition scores were normally distributed, they were analyzed using linear regression analysis. D_2FS increments were non-negative, positively skewed, and overdispersed; thus, negative binomial regression was used, which yields coefficients that have the interpretation of ln (rate ratios) as opposed to absolute differences in increment from the $D_{12}FS$ models. For purposes of presentation, these coefficients were exponentiated to yield rate ratios. In addition to the different interpretation of co-efficients from the two models, absolute differences in the two outcomes cannot be directly compared because different transition weighting matrices were used for them, which are fully explained in an associated paper (42). Nevertheless, the outcomes from these two regression models may still be contrasted, including as a test for increased trial efficiency by including non-cavitated lesions.

For each outcome measure and each interval of time, regression models were fitted that included a binary indicator of treatment status and clinical center, age, age-squared, dental cleaning history, self-fluoride use, and oral hygiene practices. Because this analysis was limited to only those individuals attending all measurement visits, all analyses were based on the same set of subjects and hence any differences in results between models cannot be attributed to differences in subjects. A parallel series of analyses were also conducted for the subset of 216 subjects whose baseline D_2FS score was 21 or higher and were thus presumed to be at higher risk of caries (44).

All analyses were conducted using SAS version 9.2 and a p-valued of 0.05 was deemed to be statistically significant.

For the primary examiners, intra-examiner reliability scores are reported based on a roughly 5% convenience sample of all participants, not just those selected for this paper, who returned for repeat examinations during the study. To assess reliability, weighted kappa statistics were computed for distinguishing S versus D_1 versus D_2 lesions. Representative kappa values are reported.

Results

The base line characteristics of the 266 xylitol and 272 placebo group subjects were similar to each other (Table 1) and to those in the full randomised sample [data not shown, (33)]. Adherence, assessed by quarterly self report, was a mean of 3.8 lozenges (range 4.3–3.3) of the target of 5 lozenges consumed the day prior, and a mean of 4.3 days (range 5.2–3.6) of the 7 prior days in which a minimum 5 or more lozenges were consumed. Adherence assessed quarterly at resupply, as cumulative lozenges dispensed as a percentage of number expected was a mean of 73.3% (range 84.2–58.3%), declining over time. These subjects had a high degree of self-reported topical fluoride exposure (≥90%), and all three sites had community water fluoridation. The intra-examiner reliability weighted kappa scores for all primary examiners for reliability in distinguishing S versus D_1 versus D_2 were as follows: baseline 0.63, 12 months 0.84, 24 months 0.66, 33 months 0.67.

The mean annual non-cavitated and cavitated lesion transition scores ($D_{12}FS$) for Xylitol and Placebo groups were contrasted with the cavitated lesion transition scores (D_2FS) for all subjects selected for this analysis, over three cumulative periods, and then annualised, Table 2. This shows mean annual difference in transition scores for $D_{12}FS$ favouring xylitol, but declining in magnitude over these time periods from −1.23 to −0.54 to −0.17. None of these differences were statistically significant. The comparable cavitated lesion (D_2FS) transition rate ratios (natural log scale) also favoured xylitol over placebo. The differences in these mean transition scores also declined over time. These rate ratio were statistically significant only in year one.

Thus, for Aim 2, the inclusion of non-cavitated and cavitated caries lesions failed to reveal a substantative and consistent effect of xylitol over placebo over three time periods; neither had the traditional cavitated lesion assessment over the full 33 months of the trial (33). Furthermore, for Aim 1, the inclusion of non-cavitated lesions did not allow this trial to reach a definitive result in a shorter time.

The result of the X-ACT trial at the cavitated lesion level (33) showed xylitol had an eleven percent but non-statistically significant caries reduction over a placebo lozenge. But when participants with higher baseline caries scores, and presumably greater caries activity, were selected for a comparable analysis, the preventive effect of xylitol at the D_2 level was found to be statistically significant over 33 months for annualised scores (33). Therefore, in parallel with this, we also studied a subsample of subjects with more severe baseline caries ($D_2FS>20$), Table 3 (n=216, xylitol group n=111 and Placebo group n=105).

This analysis of subjects with higher lifetime caries experience (Table 3) showed a mean annual difference in transition scores for $D_{12}FS$ favouring xylitol, and declining over 12, 24

and 33 months from −2.93 (p =.005) to −1.15 (p =.10) to −0.66 (p=.05). This contrasts with the analysis in these subjects for D_2FS transition scores which favoured xylitol, and declined over 12, 24 and 33 months, with the rate ratios statistically significant over 12 and 24 months only.

Therefore, under Aim 3, this analysis determined that trial subjects with greater lifetime caries experience showed an inconsistent and equivocal benefit from xylitol.

Discussion

This methodologically oriented analysis found no design efficiency by including non-cavitated lesions, either in preventive effect or time to detection. The X-ACT trial evaluated lozenges not gum as the vehicle to rule out the complex covariate effects of substantial masticatory salivary stimulation (45, 46) and possible plaque removal by mastication, that may plausibly help explain any positive effects. The trial studied effects in adults, not children or adolescents, and they were exposed to adequate fluoride. No dose response effect was reported (33). While the threshold daily dose and frequency of consumption of xylitol are not definitively determined, the most adherent subjects in this trial were consuming 5 grams/day, which is the most recent suggested threshold dose (47), so an effect could be expected to be detectable under the conditions of this trial. Furthermore, the subjects were experiencing caries throughout the trial. The measured risk reduction was of the same order at all three clinical sites. The result does not appear to have occurred due to inadequate intake or inability to detect an effect of xylitol, due to our methods. Xylitol caries risk reduction appears to be quite low in adults experiencing the disease, who also have adequate fluoride exposure.

It is possible that D_1 lesions were being retarded by xylitol earlier than at 12 months, and this was not directly detected in this trial. If xylitol had been acting to prevent lesion progress from sound to non-cavitated (D_1) or to prevent these from progressing to cavitated lesions (D_2), then assessing D_1 and D_2 lesions could be expected to show a difference over D_2 lesions alone. This was not revealed. If retardation of progress of enamel caries was occurring, then detection of this effect might have been found whether assessing D_{12} or D_2 lesions, and sooner, after 12 or 24 months rather than 33 months. A lesion retardation effect of xylitol was not observed in this study.

The observed preventive effect of xylitol diminished over cumulative time periods in this analysis for both cavitated and non-cavitated plus cavitated lesions. While absolute changes in the subjects as a whole may be influenced by regression to the mean or Hawthorne effects, treatment comparisons should be unaffected with randomization, and this bias should not affect the comparisons that are the focus of this paper. The xylitol effect was small and declined over time. It also lacked consistent statistical significance over time. If this were due to a short-term xylitol effect, then it could be expected to be more clearly evident while including non-cavitated lesions in the assessment. This was not the case. The preventive effect was nominally greater when non-cavitated lesions were included, but then the total number of lesions being assessed was greater. It has been suggested that Xylitol acts to reverse, prevent or inhibit progression of early caries. If the intervention was more

(or less) successful by including D_1 lesions in the assessment, a change in the effect size over assessment of D_2 lesions alone would be expected, but this was not found. Overall the lack of consistency in statistical significance at all time periods, the declining effect over time, and the small degree of effect are not commensurate with an interpretation of a clinically relevant preventive effect of xylitol. Any possible advantage conferred from detecting more events appears to be more than offset by added variability, as evidenced by the ever-widening confidence intervals in going from the 3-year annualized increment to the 1-year annualised increment. By contrast the CIs for the cavitated lesion analysis are fairly stable (Table 2).

Prior attempts to investigate the potential for shortening caries clinical trials by inclusion of visual and other assessments of non-cavitated lesions are not fully convincing. A successful reliability and validity study (36) involving two groups of ten examiners, involved calibration only once prior to the study proper. A comparison of the diagnostic yield of several types of visual and other examinations at the non-cavitated lesion threshold, including tooth separation, fiber optic transillumination and electronic caries measurement (in some subjects only) was made (3). The 182 Latvian children had a high caries experience, and the reliability measurements were made once only. These authors concluded that use of these alternative caries detection methods was feasible.

Alternative methods to visual caries detection hold promise of increased efficiency, but validation of these methods in detecting earlier stage lesions in full scale trials remains problematic, and additionally they must be related to the efficacy of established preventive agents assessed at the cavitated stage (6, 7). When validity is assured, examiner reliability in use of these newer detection methods will then have to be fully demonstrated under trial conditions. This dual requirement remains a very big challenge to improved trial efficiency.

In this study acceptable examiner reliability in visually assessing caries at the non-cavitated and cavitated lesions stages was attained and maintained under full clinical trial conditions. The additional effort to include non-cavitated lesions was considerable.

Assessments of non-cavitated caries lesions did not add to an understanding of the stage of lesion formation potentially affected by xylitol, and did not indicate that any shortening of this trial might have thereby been possible. This conclusion applied also to selected subjects of higher lifetime caries experience. Xylitol benefit was not shown. Enthusiasm for xylitol as a caries preventive agent in programs or for individuals should be tempered by these clinical trial findings in caries active adults with adequate fluoride exposure.

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Table 1

Sample characteristics by demography and oral health behaviours

All sites	Treatment n=266	Control n=272	Total n=538
Race/Ethnicity			
Non-Hispanic white	48.9%	52.6%	50.7%
Non-Hispanic black	27.1%	25.0%	26.0%
Hispanic	19.9%	19.5%	19.7%
Other	3.8%	2.9%	3.4%
Age	47.3 (13.4)[1]	48.8 (13.5)[1]	48.1 (13.4)[1]
Female	60.2%	67.3%	63.8%
Brushes 2+ times/day	63.2%	70.6%	66.9%
Flosses 1+ times/day	48.9%	47.8%	48.3%
Routine (exam/clean) dental visit in past year	34.2%	28.3%	31.2%
Self-report dry mouth	5.6%	9.6%	7.6%
Extent of fluoride exposure (2 mutually exclusive categories)			
Toothpaste or prof. topical fluoride	52.3%	62.9%	57.6%
Both toothpaste and prof. topical fluoride	37.6%	29.8%	33.6%
Any above topical fluoride exposure (sum)	89.9%	92.7%	91.2%

[1] data expressed as mean (Standard deviation)

Table 2

Regression results for treatment effect of xylitol vs placebo on caries increment scores* of cavitated lesions (D_2FS) and non-cavitated plus cavitated lesions ($D_{12}FS$) over three cumulative time periods, increments being annualised for each period.

Cumulative Period, Mths	Annualised D_2FS Increment Scores					Annualised $D_{12}FS$ Increment Scores				
	xylitol	placebo	RR	95% CI	p	xylitol	placebo	diff	95% CI	p
0–12	2.70	3.25	0.83	(0.71, 0.98)	0.024	3.56	4.78	−1.23	(−2.59, 0.14)	0.078
0–12 + 12–24	2.83	3.13	0.91	(0.80, 1.03)	0.118	3.50	4.05	−0.54	(−1.41, 0.33)	0.220
0–12 + 12–24 + 24–33	2.80	2.99	0.94	(0.84, 1.05)	0.264	3.46	3.63	−0.17	(−0.64, 0.30)	0.475

Regression models fit using negative binomial regression (for D_2FS increments) and standard linear regression (for $D_{12}FS$ increments) adjusting for clinical center, age, age-squared, dental cleaning history, self-fluoride use, and oral hygiene practices. The negative binomial gives rise to coefficients having the interpretation of ln (rate ratios, RR) while standard linear regression results in absolute differences in increment (diff). These differing expressions are in accordance with the differing statistical distributions of the two outcomes.

* Increment scores were derived from tables established for the trial and previously published (42).

Table 3

Regression results for treatment effect of xylitol vs placebo on caries increment scores* of cavitated lesions (D_2FS) and non-cavitated plus cavitated lesions ($D_{12}FS$) over three cumulative time periods, increments being annualised for each period, for a subset of selected participants with a baseline D_2FS of more than 20.

Cumulative Period, Mths	Annualised D_2FS Increment Scores					Annualised $D_{12}FS$ Increment Scores				
	xylitol	placebo	RR	95% CI	p	xylitol	placebo	diff	95% CI	p
0–12	2.92	3.78	0.77	(0.62, 0.97)	0.024	3.58	6.51	−2.93	(−4.98, −0.87)	0.005
0–12 + 12–24	3.39	4.09	0.83	(0.71, 0.98)	0.024	4.69	5.84	−1.15	(−2.53, 0.24)	0.104
0–12 + 12–24 + 24–33	3.52	4.02	0.88	(0.76, 1.01)	0.074	4.32	4.98	−0.66	(−1.34, 0.01)	0.053

Regression models fit using negative binomial regression (for D_2FS increments) and standard linear regression (for $D_{12}FS$ increments) adjusting for clinical center, age, age-squared, dental cleaning history, self-fluoride use, and oral hygiene practices. The negative binomial gives rise to coefficients having the interpretation of ln (rate ratios, RR) while standard linear regression results in absolute differences in increment (diff). These differing expressions are in accordance with the differing statistical distributions of the two outcomes.

* Increment scores were derived from tables established for the trial and previously published (42).